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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/509,418	07/11/2000	DONALD J KOROPATNICK	PM 266291	3674

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EXAMINER
EPPS, JANET L

ART UNIT	PAPER NUMBER
1635	27

DATE MAILED: 04/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/509,418	KOROPATNICK ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication app ars on the cover sheet with th correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 15-35 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. Evidence that claims 15-35 fail(s) to correspond in scope with that which applicant(s) regard as the invention can be found in the specification. According to the specification as filed, page 4, lines 4-7 recites "An antisense oligodeoxynucleotides is an oligonucleotide which is designed to hybridise to a specific region of a target nucleic acid sequence." Additionally, page 4, lines 28-30 of the specification as filed, recites "[T]he regions of TS mRNA targeted by the oligonucleotides *[of the invention]* are shown in Figure 7," however if you compare the oligonucleotide targeted regions of TS mRNA in Figure 7, and the antisense oligonucleotide sequences set forth in Table 1, page 5 of the specification, there is no difference between the antisense oligonucleotide sequences and the targeted sequences. In other words, the sequences according to SEQ ID NO: 1 and 2 (OLIGO 83, and OLIGO 86, respectively) contain the same sequence as the regions of TS mRNA that these oligos were designed to target, see the bracketed targeted sequences in Figure 7. Moreover, newly added claims 15-35, are drawn to compositions (or a combination thereof, and methods of use) comprising an antisense deoxyoligonucleotide having a sequence according to SEQ ID No. 1 or SEQ ID No. 2 and a pharmaceutically acceptable carrier or diluent. However,

the sequences according to SEQ ID NO: 1 and 2, do not represent antisense deoxynucleotide sequences according to Figure 7 of the specification as filed, contrary to Applicant's assertions, the sequences according to SEQ ID NO: 1-2 represent targeted regions of TS mRNA, and do not represent sequences that would hybridize "antisense" or a reverse-complement of the targeted regions of TS mRNA.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 15-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As set forth above, the sequences of the antisense deoxyoligonucleotides recited in the instant claims are not antisense sequences, instead these sequences represent the regions of TS mRNA that the antisense deoxyoligonucleotides of the present invention are targeted to. Applicants have not taught how to use the sequences according to SEQ ID NO: 1 and 2. The specification as filed does not provide sufficient guidance and/or instruction that would allow the skilled artisan to use oligonucleotides that do not hybridize to TS mRNA as "antisense deoxyoligonucleotides," or furthermore how to use these oligonucleotides in a method for inhibiting thymidylate synthase expression, or for treating cancer or an anti-proliferative effect comprising administering these oligonucleotides to a patient.

Even assuming that SEQ ID NO: 1-2 are antisense oligonucleotides, as stated in the prior Office Action, Applicants specification fails to provide sufficient guidance to the skilled artisan on the parameters for practicing a method of nucleic acid therapy in an individual *in vivo* comprising the administration of a complex comprising TS antisense oligonucleotides for the breadth of the claimed invention. Numerous factors complicate the nucleic acid based therapy, which have not been overcome by routine experimentation. These include, the controlling the fate of the nucleic acid itself once administered to an individual (volume of distribution, rate of clearance into the tissues, etc.), controlling the *in vivo* consequences of altered gene expression and protein function, the fraction of nucleic acid taken up by the target cell population, predicting the trafficking of the genetic material within cellular organelles, the rate of degradation of the nucleic acid, and the stability of the nucleic acid within a cell.

It is well established in the art that there is a significant level of unpredictability regarding the behavior of nucleic acid base therapeutics. According to Crooke (1998), states that "extrapolations from in vitro uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate". Furthermore, Crooke teaches that variations in cellular uptake and distribution of oligonucleotides are influenced by a variety of factors: length of oligonucleotide, modifications, sequence of oligonucleotide and cell type. Crooke also states that protein binding in general by nucleic acid based therapeutics may influence cell uptake, distribution, metabolism and excretion of the oligonucleotide. Furthermore, such protein binding may produce effects that can be mistakenly interpreted as the result of the nucleic acid alone. In addition to proteins, nucleic acids may interact with other biological molecules, such as lipids, or carbohydrates, and such interactions, like those with proteins, will be influenced by the chemical

class of oligonucleotide studied (Crooke, 1998; p. 3). Crooke clearly teaches that there is a significant level of factors which influence the behavior of nucleic acid based compounds thereby rendering the activity and behavior of nucleic acid based therapeutics unpredictable, and thus much experimentation is required to screen multiple nucleic acid compounds to determine not only their efficacy *in vitro* but also *in vivo*.

Additionally, the specification does not provide any working examples that enable the claimed invention. Nor does the specification provide any guidance to the skilled artisan on how to make and use the claimed TS antisense oligonucleotides, which would produce a desired effect, namely for use in treating a patient in need of therapy. Even assuming that an effective TS antisense oligonucleotide is constructed, it is not evident that enough cells can be transfected to provide any therapeutic benefit.

The amount of experimentation necessary to practice the claimed invention would require providing a means to deliver the TS antisense oligonucleotides to the correct target tissues associated with said disease or condition in a sufficient amount and duration, so as to produce a desired therapeutic result. Such guidance is not provided in the specification as filed or in the prior art of record at the time of filing of the instant application. Furthermore, a development of this scale in the unpredictable nucleic acid therapy art would have been considered to necessitate undue experimentation on the part of the skilled practitioner.

Therefore, the specification as filed does not describe the use of TS antisense oligonucleotides in a method of nucleic acid therapy, in a sufficient manner so as to enable one of ordinary skill in the art to practice the present invention without undue experimentation. This conclusion is based upon the known unpredictability regarding the behavior of nucleic acid

based therapeutics *in vivo* and further with the production of the desired secondary effects, such as treating a patient in need of therapy, and the lack of guidance in the specification as filed in this regard.

Conclusion

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on M-T, Thurs-Friday 9:00AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703)-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE
April 12, 2003

SEAN McGARRY
PRIMARY EXAMINER
1635